Human induced pluripotent stem cell-derived macrophages ameliorate liver fibrosis.

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Public Summary:
Chronic toxic liver injury due to various etiologies including viral infection (hepatitis B and C), metabolic disorders (nonalcoholic) myofibroblasts which secrete extracellular matrix (ECM) proteins and result in a fibrous scar. Liver fibrosis progresses to cirrhosis, hepatocellular carcinoma, and eventual liver failure where organ transplantation is the only treatment option. An alternative therapy is transplantation of cells that enable liver repair and/or regeneration. Transplantation of myeloid cells alone or in combination with mesenchymal stem/stromal cells (MSCs) have been shown to suppress inflammatory responses, and as a result, lead to the improvement of liver function. Infusion of autologous macrophages in patients with end stage liver disease has also shown promise in clinic. Several other cell types have shown efficacy in preclinical models, including hepatocytes, liver sinusoidal endothelial cells, and endothelial progenitor cells. Improved treatment for diseased or degenerated tissues and organs is greatly needed. These studies demonstrate the ability to efficiently derive macrophages from human induced pluripotent stem cells (iPSCs) with the ability to improve liver fibrosis in a mouse xenograft model. The present study enables clinical translation to use these iPSC-derived cells to better treat diverse fibrotic diseases. Future studies are important to now translate human iPSC-derived macrophages into clinical therapies for tissue repair and regeneration.

Scientific Abstract:
With an increasing number of patients with degenerative hepatic diseases, such as liver fibrosis, and a limited supply of donor organs, there is an unmet need for therapies that can repair or regenerate damaged liver tissue. Treatment with macrophages that are capable of phagocytosis and anti-inflammatory activities such as secretion of matrix metalloproteinases (MMPs) provide an attractive cellular therapy approach. Human induced pluripotent stem cells (iPSCs) are capable of efficiently generating a large-scale, homogenous population of human macrophages using fully defined feeder- and serum-free differentiation protocol. Human iPSC-macrophages exhibit classical surface cell markers and phagocytic activity similar to peripheral blood-derived macrophages. Moreover, gene and cytokine expression analysis reveal that these macrophages can be efficiently polarized to pro-inflammatory M1 or anti-inflammatory M2 phenotypes in presence of LPS + IFN-gamma and IL-4 + IL-13, respectively. M1 macrophages express high level of CD80, TNF-alpha, and IL-6 while M2 macrophages show elevated expression of CD206, CCL17, and CCL22. Here, we demonstrate that treatment of liver fibrosis with both human iPSC-derived macrophage populations and especially M2 subtype significantly reduces fibrogenic gene expression and disease associated histological markers including Sirius Red, alphaSMA and desmin in immunodeficient Rag2(-/-) gammac(-/-) mice model, making this approach a promising cell-based avenue to ameliorate fibrosis.